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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/626,879

07/25/2003

Jang Han

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NOVARTIS VACCINES AND DIAGNOSTICS INC.

INTELLECTUAL PROPERTY- X100B

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EXAMINER

ZARA, JANE J

ART UNIT

PAPER NUMBER

1635

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DELIVERY MODE

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/626,879	<b>Applicant(s)</b> HAN ET AL.	
	<b>Examiner</b> Jane Zara	<b>Art Unit</b> 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 09 April 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-7,14,15,17-20,24,25,43,45-56,67-74,81,84,87 and 89-91 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-7,14,15,17-20,24,25,43,45-56,67-74,81,84,87 and 89-91 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)         | 4) <input type="checkbox"/> Interview Summary (PTO-413)                 |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application       |
| Paper No(s)/Mail Date _____   | 6) <input checked="" type="checkbox"/> Other: <u>Seq Alignment Data</u> |

### **DETAILED ACTION**

This Office action is in response to the communication filed 4-9-10.

Claims 1, 2, 4-7, 14, 15, 17-20, 24, 25, 43, 45-56, 67-74, 81, 84, 87, 89-91 are pending in the instant application.

### ***Priority***

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e), 120, 121, or 365(c) as follows: SEQ ID Nos. that are specifically claimed have no support in the provisional applications listed as priority documents. For this reason, the pending claims are entitled to a priority date of 7-25-03.

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-8-10 has been entered.

***Election/Restrictions***

Applicant's election with traverse of SEQ ID No. 12, as it pertains to claims 1, 2, 4-7, 14, 15, 17-20, 24, 25, 43, 45-56, 67-74, 81, 84, 87, 89-91, in the reply filed on 4-9-10 is acknowledged. The traversal is on the ground(s) that all of the groups (compositions and methods) have been examined previously and that no undue burden exists to examine all of the sequences and Groups claimed. This is not found fully persuasive because an undue burden indeed exists in searching all of the sequences claimed. This in light of the multitude of data bases that must be searched to properly examine each and all of the individual sequences claimed.

The requirement is still deemed proper and is therefore made FINAL.

Sequences other than SEQ ID NO. 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4-9-10.

***Response to Arguments and Amendments***

***Withdrawn Rejections***

Any rejections not repeated in this Office action are hereby withdrawn.

Applicant's arguments with respect to claims 1, 2, 4-7, 14, 15, 17-20, 24, 25, 43, 45-56, 67-74, 81, 84, 87, 89-91 have been considered but are moot in view of the new ground(s) of rejection.

New Rejections

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 4-7, 14, 15, 17-20, 24, 25, 43, 45-56, 67-74, 81, 84, 87, 89-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wands et al (USPN 6,001,990), Draper et al (WO 93/23569), and Lemon et al (US 2002/0155582), the combination in view of Fire et al (USPN 6,506,559), the combination further in view of Fosnaugh et al (US 2003/0143732), Morrissey et al (US 2003/0206887) and McKay et al (USPN 6,133,246), and Alsobrook et al (US 2003/0219823) for the reasons of record set forth in the Office action mailed 12-9-08.

The claims are drawn to compositions and methods of making a modified siRNA, methods of inactivating, inhibiting and/or treating hepatitis C virus (HCV) comprising administration of siRNA sharing at least 95% to 99% identity with SEQ ID NOs. 12-27, which target and inhibit nucleic acids encoding HCV, and which siRNA further comprise 2'-fluoro or 2'-O-methyl modified groups, a modified cytosine, which siRNA are optionally expressed via an expression vector, and which siRNA are operatively linked to a first and second promoter, comprising a U6 and H1 promoter, and which siRNA optionally further comprise modified internucleotide linkages.

Wands et al (USPN 6,001,990) teach the inhibition of HCV RNA translation comprising the administration of an antisense oligonucleotide that specifically targets nucleic acids encoding HCV, and which antisense comprises at least 95% to 99% identity with SEQ ID NO. 12 (See esp. the abstract, col. 1-8, 10-17; AR094972 and accompanying alignment data with the instantly claimed SEQ ID NO. 12).

Draper et al (WO 93/23569) teach the inhibition of HCV RNA translation comprising the administration of an inhibitory oligonucleotide that specifically targets nucleic acids encoding HCV, and which comprises at least 95% to 99% identity with SEQ ID NO. 12 (See Claim 5, figure 12, and Accession No. AAQ52822, and accompanying alignment data with the instantly claimed SEQ ID NO. 12).

Lemon et al (US 2002/0155582) teach an oligonucleotide that targets nucleic acids encoding HCV, and which comprises at least 95% to 99% identity with SEQ ID NO. 12 (See SEQ ID No. 1, and accompanying alignment data with the instantly claimed SEQ ID NO. 12).

The primary references of Wands, Draper and Lemon do not teach siRNA molecules for inhibiting HCV infections, nor all of the modifications instantly claimed, or the use of U6 and H1 promoters to drive expression of siRNA in an appropriate expression vector.

Fire et al (USPN 6,506,559) teach the use of inhibitory oligonucleotides in inhibiting the expression of target genes in vitro and in vivo. Fire teaches the advantages of using siRNA for target gene inhibition compared to other inhibitory oligonucleotides, including antisense and ribozymes, and teaches the use of expression

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vectors for expressing siRNA molecules in an organism. Fire also teaches the incorporation of modified internucleotide linkages and modified nucleotides into siRNA molecules for enhancing oligonucleotide stability, target binding and cellular uptake (see the abstract; col. 1-5, 7; claims 1-6, 10, 21).

Alsobrook et al (US 2003/0219823) teach expression vectors comprising U6 or H1 for expression of siRNA in an appropriate target cell (see esp. paragraph 0090).

Fosnaugh et al (US 2003/0143732) teach various motifs and configurations of 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini, and the effect of arrangements of these different modifications on siRNA ability to bind to and inhibit target gene expression in the presence of RISC. Fosnaugh et al also teach compositions comprising modified and unmodified siRNAs and RISC for target gene inhibition see p. 1, 3-4, 6-9, p. 16 and figures 4 and 5, claim 30).

Morrissey et al (US 2003/0206887) teach various ways of designing and optimizing 2'-modifications on siRNA, including 2'-fluoro or methoxyalkyl groups of various alkyl chain lengths, and abasic, inverted abasic termini and 5' and 3' capped termini, and the effect of various motifs or arrangements of these 2'-substitutents and modified phosphorothioate internucleotide linkages on target gene inhibition by siRNA in

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compositions further comprising RISC (see fig. 4 and 5, page 1, right col., p. 6, right col., p. 9, p. 20-21, claims 20-25).

McKay et al (USPN 6,133,246) teach numerous motifs and combinations of modified residues within antisense oligonucleotides, including the incorporation of 2'-modified sugars which include 2'-fluoro, 2'-bromo, 2'-O-alkyl groups, modified nucleobases including modified cytosines, modified internucleotide linkages, 2'- $\beta$ -D-deoxynucleosides and combinations thereof, as well as the optimization of modifications for maximizing target binding, cellular uptake and oligonucleotide stability (see esp. col. 7-12; Tables 4-26, esp. Tables 11 and 12, and Table 26).

It would have been obvious to design and utilize siRNA molecules that share at least 95-99% identity with SEQ ID NO. 12 for inhibiting HCV replication and HCV infection because antisense and other inhibitory oligonucleotides comprising this sequence identity were well known in the art at the time the instant invention was made, as illustrated by the teachings of Wands, Draper and Lemon, and siRNA molecules were well known in the art to target and inhibit a target gene of known sequence more efficiently than antisense or ribozymes, as taught previously by Fire. One would have been motivated to utilize siRNA molecules comprising SEQ ID No. 12 because this target region of the HCV sequence were well known to be accessible to antisense oligonucleotides, and siRNA were known to be more effective inhibitors of target gene expression.

One would have been motivated to inhibit the expression or replication of HCV because HCV infections are known to cause deleterious effects in humans, as taught



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previously by many in the art, including Wands, Draper and Lemon. One of ordinary skill would have reasonably expected to utilize the inhibitory oligonucleotides, previously taught and tested by Wands, Draper and Lemon, in siRNA constructs and achieve target gene inhibition because of the known advantages of siRNA, as taught previously by Fire et al, and the accessibility of this target region of HCV was also well known in the art, as previously disclosed by Wands, Draper and Lemon.

One of ordinary skill in the art would have been motivated to express siRNA molecules, either as a single, self-complementary molecule, or as two separate strands, because expression of siRNA within a cell from an appropriate expression vector provides increased siRNA within a target cell. One of ordinary skill in the art would have been motivated to use the well known and reliable U6 and H1 promoters to drive expression in an appropriate expression vector because these promoters are well known in the art to provide for predictable and high expression of siRNA in a target cell, as taught previously by AlsoBrook et al.

It would have been obvious to incorporate 2'-modifications, including fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to different motifs of differing 2'-substituent containing motifs, internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and which oligonucleotides optionally further comprise modified nucleobases, including modified cytosines into siRNA molecules for enhancing their target binding and stability, yet minimizing inactivation of the siRNA ability to inhibit target gene expression because Fosnaugh, Morrissey, Fire and McKay all teach the

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advantages of incorporating these modifications into inhibitory oligonucleotides for enhancing target gene binding, cellular uptake and oligonucleotide stability. One of ordinary skill would have expected that the incorporation of these modifications are optimized using routine experimentation, and one of ordinary skill in the art would have expected that the siRNA molecules, modified as instantly claimed, would provide target gene cleavage in the presence of an appropriate target gene sequence and in the presence of appropriately modified siRNA. One of ordinary skill in the art would have reasonably expected that these modifications would provide for the advantages previously taught, of enhancing target binding and oligonucleotide stability, and would lead to improved target gene inhibition.

For these reasons in the instant invention would have been obvious to one of skill at the time of filing.

### ***Conclusion***

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**.

The examiner's office hours are usually Monday - Friday, 10:30am – 7:00pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi, can be reached on (571) 272-3311. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**Jane Zara**  
**5-6-10**

/Jane Zara/

Primary Examiner, Art Unit 1635